

Application No.: 10/766,106

Docket No.: PRJ-006CN

REMARKS

Claims 1-22 are pending in the present application. These claims have not been amended in the present response, and are believed to be in condition for allowance for at least the following reasons.

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Rejection of Claims 1-11 and 21 Under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 1-11 and 21 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner is of the opinion that the phrase "predominantly a single species" of claim 21 is unclear, because "[w]hile it is understood that the term 'species' itself is art recognized, the term itself is never described in terms in which the ordinary practitioner would have been able to make and use the invention as described." In addition, the Examiner rejects claim 1 on the basis that the claimed phrase "predominantly a single site on the interferon" is not found in the original specification, and, therefore, constitutes new matter. Applicants respectfully traverse this rejection.

I. With respect to the rejection of claim 21 based on clarity of the term "predominantly a single species," the Examiner has acknowledged that "the term 'species' itself is well known in the art. Thus, the term "predominantly a single species" would also be clear to one of ordinary skill in the art based on the plain and ordinary meaning of the terms "predominantly" (*i.e.*, substantially) and "single" (*i.e.*, one). Indeed, the term "single species" was well known in the art at the time of filing to mean that each conjugated (*e.g.*, PEGylated) molecule within the composition is conjugated in the same manner (*e.g.*, at the same site or sites on the molecule), thereby forming a homogenous mixture of molecules, *i.e.*, substantially one type of conjugated species. Applicants' specification is entirely consistent with this art-recognized definition in that it provides several working examples which describe how to make and use pharmaceutical formulations comprising predominantly single species of PEGylated molecules (see Examples 1-19 which teach various bioactive molecules which are PEGylated in a uniform manner, thus forming a single species (*i.e.*, homogenous population) of PEGylated molecules), as claimed. Therefore, the meaning of "predominantly single species" would be more than clear to one of ordinary skill in the art. Furthermore, Applicants' had possession of the subject matter of claim 21 at the time the present application was filed.

In particular, in the present application, Applicants have described the preparation, characterization and administration of Leu-enkephalin (PEGylated at one site; see Examples 1-

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6), Biphalin (PEGylated at two sites; see Examples 7-12), and insulin (PEGylated at three sites; see Example 13), all of which were PEGylated in a uniform manner, resulting in the formation of predominantly a single species of PEGylated molecules. In Example 1, 25 mg Leu-enkephalin was reacted with 250 mg mPEG(5000)-SPA in DMSO/triethylamine. Leu-enkephalin is known to have a single amino group at the peptide amino terminus. Analysis by reversed phase(RP) HPLC of the isolated reaction product showed >95% pegylation and therefore resulted in >95% of a single species, *i.e.*, the reaction product was predominantly a single species (see page 8, lines 14-15 of the specification). Since Leu-enkephalin has only one site available for reaction with the PEG reagent, it will be appreciated that Example 1 also demonstrates that the product was linked "predominantly at a single site."

Examples 7-12 disclose the preparation, characterization and administration of compositions for delivering Biphalin, wherein two specific sites on each molecule are PEGylated (since Biphalin has only two sites available for PEGylation). Thus, Biphalin (supplied by a collaborator) was also shown to be predominantly a single species, as each of the 2 amino groups per molecule was PEGylated using mPEG(5000)-SPA. The product was shown to be pure by RPHPLC (M. Bentley *et al.* Abstract # 7121, *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, 2001).

As described in Example 13, insulin (116 mg) was reacted with 1 gm mPEG(5000)-SPA in DMSO/triethylamine. The analysis of the isolated reaction product by RPHPLC showed >95% pegylated product (page 14, lines 22-23 of the specification). This result, along with the excess of reagent used, can only be interpreted to show that essentially all the insulin amino groups have been derivatized, and thus the product is predominantly a single species, namely tri-mPEG(5000)-insulin.

Accordingly, based on the multiple Examples provided in Applicants' description, and the consistent art-recognized meaning of the term "predominantly a single species," it would be clear to one of ordinary skill in the art that Applicants had full possession of the subject matter of claim 21.

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II. With respect to the rejection of claims 1-11 based on lack of literal support for the phrase “predominantly a single site on the interferon,” it is well established that verbatim literal support need not be present in the specification if the claimed invention is described in a manner which sufficiently demonstrates to one of ordinary skill that the inventors had possession of the invention at the time of filing. See *In re Lukach*, 442 F.2d 967, 969, 169 USPQ 795 (C.C.P.A. 1971) (an invention need not be described in *ipsis verbis* to satisfy description requirement of 35 U.S.C. § 112); *In re Wertheim*, 541 F.2d 257, 262 and 265, 191 USPQ 90 (C.C.P.A. 1976) (“lack of literal support” is insufficient to support a rejection under 35 U.S.C. § 112), appeal after remand 646 F.2d 527, 209 USPQ 554 (C.C.P.A. 1981); *In re Hayes Microcomputer Products Inc. Patent Litigation*, 982 F.2d 1527, 1533, 25 USPQ2d 1241, (Fed. Cir. 1992) (noting exact description of subject matter is not necessary, as long as “persons of ordinary skill in the art recognize” that applicant invented what is claimed); MPEP § 2163.

As discussed above and further below, based on the description and Examples provided in Applicants’ disclosure of conjugates which are PEGylated at predominantly a single site, it would be more than clear to one of ordinary skill that Applicants’ had possession of the invention encompassed by claims 1-11 at the time of filing. Moreover, it is also well established that *the express description of an inherent property does not constitute new matter* and can be added to the specification with effect as of the original filing date. See *In re Nathan*, 51 C.C.P.A. 1059, 328 F.2d 1005, 1008-09, 140 U.S.P.Q. (BNA) 601, 604 (C.C.P.A. 1964) (amendment which defines more precisely an inherent characteristic of the claimed subject matter for those skilled in the art is not new matter); *In re Reynolds*, 58 C.C.P.A. 1287, 443 F.2d 384, 170 U.S.P.Q. (BNA) 94 (C.C.P.A. 1971) (application may be later amended to recite inherent feature of claimed invention, without introducing prohibited new matter); *Kennecott Corp. v. Kyocera International, Inc.*, 835 F.2d 1419, 1422, 5 USPQ2d 1194, 1197 (Fed. Cir. 1987) (subsequent inclusion of existing physical structure to describe inherent feature is not new subject matter), cert. denied, 486 U.S. 1008 (1988). In *In Re Nathan* the U.S. Court of Customs and Patent Appeals (C.C.P.A.) addressed this issue and held that Appellants’ amendment specifying the alpha configuration was not new matter and instead merely a statement of an inherent property of the steroids as originally disclosed. The C.C.P.A. relied on Appellants’ description of the products of the invention as adequately demonstrating an inherent characteristic (the alpha orientation) of Appellants’ claimed subject matter.

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In the present case, Applicants disclosure describes conjugates which are PEGylated at predominantly a single site and, thus, inherently have the property recited in claims 1-11. Accordingly, this feature need not have been described literally in the specification as originally filed. For instance, as described in detail above, Examples 1-6 teach the generation of Leu-enkephalin conjugates which are PEGylated at predominantly one site. Given this description, it would be clear to one of ordinary skill in the art that Applicants had possession of the claimed invention at the time of filing, and that the subject matter of claims 1-11 does not constitute new matter.

For at least the reasons provided above, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejection of Claims Under 35 U.S.C. §102(b)

The Examiner rejects claim 21 under 35 U.S.C. §102(b) as being anticipated by Lam *et al.* (Controlled Release Society 30th Annual Meeting - 2003), Kim *et al.* (*Biomaterials*, 23:2311-2317 (2002)), and Kim *et al.* (*Proceed Int'l. Symp. Control. Rel. Bioact. Mater.*, Controlled Release Society, 28 (2001)). The Examiner further rejects claims 1-18 under 35 U.S.C. §102(b) as being anticipated by Diwan *et al.* (*International Journal of Pharmaceutics*, 252:111-122(2003)).

Applicants respectfully traverse this rejection. The present application claims priority to U.S. Serial No. 60/244,499, filed October 31, 2000. For at least the reasons provided above in response to the rejections under §112, first paragraph, all of the claims of the present application are entitled to the full benefit of this priority date. Accordingly, Lam *et al.*, Kim *et al.* (2002), Kim *et al.* (2001) and Diwan *et al.*, all of which were published after October 31, 2000, are not available as prior art against the claims of the present application. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

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Rejection of Claims Under 35 U.S.C. §103

The Examiner has rejected claim 22 under 35 U.S.C. §103(a) as being unpatentable over Kim *et al.* (2001).

Applicants respectfully traverse this rejection. As discussed above, the presently pending claims are entitled to the benefit of priority to U.S. Serial No. 60/244,499, filed October 31, 2000. Therefore, Kim *et al.* (2001) is not available as prior art against claim 22. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

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CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

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Respectfully submitted,

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